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(71) Applicant *(for all designated States except US)*: ALCON LABORATORIES, INC. [US/US]; 6201 South Freeway, Fort Worth, TX 76134–2099 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: DEAN, Thomas, R. [US/US]; 101 Meadow View Court, Weatherford, TX 76087 (US). MAY, Jesse, A. [US/US]; 4132 Hildring Drive East, Fort Worth, TX 76109 (US).

(74) Agents: YEAGER, Sally, S. et al.; Alcon Laboratories, Inc., Patent Dept., Q–148, 6201 South Freeway, Fort Worth, TX 76134–2099 (US).

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(54) Title: USE OF A COMBINATION OF CARBONIC ANHYDRASE INHIBITORS AND PROSTAGLANDINS FOR TREATING GLAUCOMA

(57) Abstract

Compositions and methods for treating persons suffering from glaucoma or ocular hypertension are disclosed. In particular, the persons are treated with prostaglandins and carbonic anhydrase inhibitors to control their intraocular pressure.

FOR THE PURPOSES OF INFORMATION ONLY

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USE OF A COMBINATION OF CARBONIC ANHYDRASE INHIBITORS AND PROSTAGLANDINS FOR TREATING GLAUCOMA

Background of the Invention

The present invention relates to the field of ophthalmology. In particular, the invention relates to the treatment of persons suffering from glaucoma and associated elevations of intraocular pressure (IOP) and/or ocular hypertension.

Although the underlying causes of glaucoma are not understood, its symptoms often include elevated IOP, which may be caused either by over-production or inadequate outflow of aqueous humor. If left untreated, or if inadequately treated, glaucoma can lead to blindness or significant loss of vision. There is therefore a continuing need for therapies which control the elevated intraocular pressure associated with glaucoma.

There are currently a number of drugs used in the treatment of glaucoma and ocular hypertension, including: miotics (e.g., pilocarpine, carbachol, and acetylcholinesterase inhibitors); sympathomimetics (e.g., epinephrine, dipivalylepinephrine, and para-amino clonidine); beta-blockers (e.g., betaxolol, levobunolol, and timolol); and carbonic anhydrase inhibitors (CAIs) e.g., acetazolamide, methazolamide and ethoxzolamide systemically and dorzolamide topically. Prostaglandins (PGs) are currently being developed for use in treating persons with glaucoma and the PG, latanoprost, marketed as Xalatan®, is available from Pharmacia-Upjohn.

Miotics and sympathomimetics are believed to lower IOP by increasing the outflow of aqueous humor, while beta-blockers and carbonic anhydrase inhibitors are believed to lower IOP by decreasing the formation of aqueous humor. All four types of drugs have

potentially serious side effects. Miotics, such as pilocarpine, can cause brow ache, blurring of vision, and other visual side effects, which may lead either to decreased patient compliance or to therapy termination. Systemically administered carbonic anhydrase inhibitors can also cause serious side effects which affect patient compliance and/or necessitate the withdrawal of treatment. Beta-blockers can be irritating. Sympathomimetics can cause allergic responses and sedation. Side effects associated with PGs include edema, hyperemia, and foreign body sensation.

A significant number of glaucoma patients require the administration of more than one type of drug in order to achieve therapeutic control over their IOP because a single drug does not provide adequate IOP control. The use of two drugs, each of which affects IOP by a different mechanism, would be useful in treating these patients. The present invention is directed to such use, either by administration of the drugs separately or in combination.

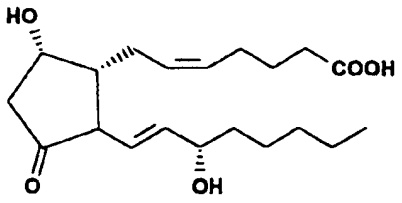
Summary of the Invention

The present invention is directed to methods for treating patients with glaucoma or ocular hypertension wherein their IOP can only be controlled by the use of two IOP lowering drugs, namely, carbonic anhydrase inhibitors and prostaglandins. These drugs may be dosed simultaneously or at different times and may also be formulated in a single composition to provide for convenience and patient compliance.

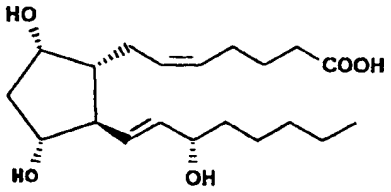
Detailed Description of the Invention

Prostaglandins are metabolic derivatives of arachidonic acid. The arachidonic acid cascade is initiated by the conversion of arachidonic acid to prostaglandin G_2 and its subsequent conversion to prostaglandin H_2. Other naturally occurring prostaglandins are derivatives of prostaglandin H_2. A number of different types of prostaglandins have been discovered including A, B, D, E, F and I-Series prostaglandins.

The prostaglandins which are useful according to the present invention include all prostaglandins which exhibit similar IOP lowering mechanisms as PGD_2(I) or $PGF_{2\alpha}$(II):



(I)



(II)

While Applicants do not wish to be bound by any theory, the D-prostaglandins ("DP-agonist") are believed to inhibit aqueous humor formation and may have an affect on its outflow. F-prostaglandins ("FP-agonist") are believed to increase the outflow of aqueous humor from the eye.

The DP-agonists of the present invention are useful in lowering IOP in humans and other mammals. The DP-agonists of the present invention are functionally defined by their ability to bind to prostaglandin-D_2 receptors of cells and evoke similar responses as when PGD_2 binds to these receptors inducing the lowering of IOP. Various assays may be used for the determination of DP-agonists.

Binding assays may be used to elucidate DP-agonists of the present invention. Sharif, et al. have described a receptor binding assay in: Sharif, N.A., Williams, G.W. and DeSantis, L.M, Neurochemistry Research, volume 20, pages 669-674 (1995), the entire contents of which are incorporated herein by reference, and may be modified as described below, for the elucidation of DP-agonists of the present invention. Briefly, the binding assays are conducted in 25 mM Tris HCl (pH 7.4) containing 138 mM NaCl, 5 mM $MgCl_2$, and 1 mM EDTA. Frozen-thawed expired human blood platelets (40-60 mg/ml stock) are incubated in a total volume of 500 ml with 2-10 nM [^{3}H]PGD_2 in the absence

and presence of 100 mM unlabeled PGD_2 to define total and non-specific binding, respectively. The incubations (20 minutes at 23°C) are terminated by rapid vacuum filtration, using a Whatman GF/B glass fiber filter previously soaked in 1% polyethyleneimine and 0.1% BSA, and the receptor-bound radioactivity is then determined by scintillation spectrometry. The binding data are analyzed using a non-linear, iterative curve-fitting computer program to define the receptor binding affinity (K_i) of the compounds. Compounds which exhibit K_i values in this assay of less than or equal to about 20 μM are within the definition of DP-agonists of the present invention.

The DP-agonists of the present invention may also be defined functionally, by their ability to stimulate adenylate cyclase activity. Sharif, et al. have described this type of functional assay in: Sharif, N.A., Xu, S. and Yanni, J.M., Journal of Ocular Pharmacology, volume 10, pages 653-664 (1994), the entire contents of which are incorporated herein by reference, and which may be modified as described below, for the elucidation of DP-agonists of the present invention. Briefly, functional adenylate cyclase activity is determined using embryonic bovine tracheal cells (EbTr) cells. Cultured cells are stimulated with the test compound for 15 minutes at 23°C. The reaction is then stopped and the cAMP generated is determined by a radioimmunoassay kit. Data are analyzed using a non-linear, iterative curve-fitting computer program to define the potency ("EC_{50}", concentration which produces 50% of the maximum response of PGD_2) and efficacy of the compounds. Compounds which exhibit EC_{50} values of less than or equal to about 10 mM are within the DP-agonist definition of the present invention.

Preferred DP-agonists include: [1R-[1.α.(Z),2.ß.(1E,3S),3.α.,5.α.]]-[[4-[5-chloro-2-(3-cyclohexyl-3-hydroxy-propyl)-3-hydroxycyclopentyl]-2-butenyl]oxy]-acetic acid, t-butyl ester (see EP0299 914B1) and ([1R-[1.α.(Z),2.ß.(3S),3.α.,5.α.]]-[[4-[5-chloro-2-(3-cyclohexyl-3-hydroxy-propyl)-3-hydroxycyclopentyl]-2-butenyl]oxy]-acetic acid, isopropyl ester) (see commonly assigned U.S. Patent No. 5,627,209).

Preferred FP-agonists include: latanoprost (Xalatan®, available from Upjohn-Pharmacia) (see U.S. Patent No. 5,296,504), and the compounds disclosed in U.S. Patent No. 5,510,383, particularly isopropyl esters of cloprostenol and fluprostenol and their individual isomers and the compounds disclosed in WO 97/23223. Most preferred compounds are (+)-isopropyl fluprostenol and compound VIII on page 9 of WO 97/23223 (Isopropyl [2R(1E,3R),3S(4Z),4R]-7-[Tetrahydro-2-[4-(3-chlorophenoxy)-3-hydroxy-1-butenyl]-4-hydroxy-3-furanyl]-4-heptenoate).

The CAIs which are useful in the compositions and methods of the present invention include all thiophene sulfonamides and thienothiazines which lower and control IOP by inhibiting carbonic anhydrase when administered topically. Representative CAIs are disclosed in: U.S. Patent Nos. 4,797,413 (Baldwin, et al.), 4,847,289 (Baldwin, et al.), and 4,731,368 (Hoffman, Jr., et al.); U.S. Patent Nos. 5,153,192 (Dean, et al.), 5,240,923 (Dean, et al.), and 5,378,703 (Dean, et al.); PCT/US91/02262 (filed 9 April 1990); and EP 452 151 (published 16 October 1991). The entire contents of each of the above-mentioned patents and patent applications are incorporated herein by reference.

Preferred CAIs of the present invention are those disclosed in U.S. Patent No. 5,378,703, particularly, R-(+)-4-ethylamino-3,4-dihydro-2-(3-methoxypropyl)-2H-thieno[3,2,e]-1,2-thiazine-6-sulfonamide-1,1-dioxide (brinzolamide).

The PGs and CAIs of the present invention may be formulated either separately or in the same pharmaceutical compositions. Thus, they can be administered simultaneously or sequentially to humans and other mammals suffering from glaucoma or ocular hypertension. When formulated separately the drugs may be administered 1) concomitantly; 2) within a short delay between one agent and the other; or 3) in an offset manner. It is preferred that the PG be dosed at night.

In general, the PG concentration in a formulation is between about 0.00005 and about 0.5 percent by weight (wt.%), preferably between about 0.0003 and 0.3% wt.%,

most preferably between about 0.0005 and 0.03 wt.%. The CAI concentration in a formulation is between about 0.1 and 10.0 wt.%, preferably between about 0.25 and 3 wt.%, most preferably between about 0.5 and 2.0 wt.%. In a combination formula, the PG concentration can be between 0.0005 and 0.03 wt.% and the CAI 0.5 and 1.5 wt.%.

In addition to the above-described principal ingredients, the anti-glaucoma compositions of the present invention may further comprise various formulatory ingredients, such as antimicrobial preservatives and tonicity agents. Examples of suitable antimicrobial preservatives include: benzalkonium chloride, thimerosal, chlorobutanol, methyl paraben, propyl paraben, phenylethyl alcohol, edetate disodium, sorbic acid, Onamer M® and other agents equally well-known to those skilled in the art. Such preservatives, if used, will typically be employed in an amount between about 0.001 to 1.0 wt.%. Examples of suitable agents which may be used to adjust the tonicity or osmolality of the formulations include: sodium chloride, potassium chloride, mannitol, dextrose, glycerin, and propylene glycol. Such agents, if used, will typically be employed in an amount between about 0.1 to 10.0 wt%. Also, viscosity enhancers, such as hydroxyethyl cellulose, hydroxypropyl methyl cellulose, and carbomers, may be used, and when they are, the prostaglandin concentration can be substantially reduced. Stabilizing agents may also be employed, such as, polyethoxylated castor oils like cremaphor EL.

As will be appreciated by those skilled in the art, the compositions may be formulated in various dosage forms suitable for topical ophthalmic delivery, including solutions, suspensions, emulsions, gels, and erodible solid ocular inserts. Combination compositions preferably are aqueous suspensions, have a pH between 5.0 to 7.8, preferably 6.5 to 7.6, and an osmolality between 280 to 320 milliOsmoles per kilogram (mOsm/kg).

The following examples further illustrate the anti-glaucoma compositions of the present invention, but are not limiting.

Example 1

Ophthalmic Suspension

Ingredient	Concentration (wt %)
Brinzolamide	1.0
([1R-[1.α.(Z),2.ß.(3S),3.α.,5.α.]]-[[4-[5-chloro-2-(3-cyclohexyl-3-hydroxy-propyl)-3-hydroxycyclopentyl]-2-butenyl]oxy]-acetic acid, isopropyl ester)	0.01
Hydroxypropylmethylcellulose	0.5
Dibasic Sodium Phosphate	0.2
Disodium Edetate	0.01
Sodium Chloride	0.8
Purified Water	q.s
Benzalkonium Chloride	0.01
Cremaphor	0.1
NaOH/HCl	pH 7.1

Exampl 2

Ophthalmic Suspension

Ingredient	Concentration (wt %)
Brinzolamide	1.0
(+)-Isopropyl Fluprostenol	0.005
Hydroxypropylmethylcellulose	0.5
Dibasic Sodium Phosphate	0.2
Disodium Edetate	0.01
Sodium Chloride	0.8
Purified Water	q.s
Benzalkonium Chloride	0.01
Cremaphor	0.1
NaOH/HCl	pH 7.1

Example 3

Ophthalmic Suspension

Ingredient	Concentration (wt %)
Brinzolamide	1.0
Isopropyl [2R(1E,3R),3S(4Z),4R]-7-[Tetrahydro-2-[4-(3-chlorophenoxy)-3-hydroxy-1-butenyl]-4-hydroxy-3-furanyl]-4-heptenoate	0.01
Hydroxypropylmethylcellulose	0.5
Dibasic Sodium Phosphate	0.2
Disodium Edetate	0.01
Sodium Chloride	0.8
Purified Water	q.s
Benzalkonium Chloride	0.01
Cremaphor	0.1
NaOH/HCl	pH 7.1

Example 4

An example of two formulations to be used concomitantly, within 30 minutes, or offset by more than 1 hour.

Formulation A

Ingredient	Amount (wt%)
(+)-Isopropyl Fluprostenol	0.005
Monobasic sodium phosphate	0.05
Dibasic sodium phosphate (anhydrous)	0.15
Sodium chloride	0.75
Disodium EDTA (Edetate disodium)	0.05
Cremophor EL	0.1
Benzalkonium chloride	0.01
HCl and/or NaOH	pH 7.3 - 7.4
Purified water	q.s. to 100%

Formulation B

Ingredient	Concentration (wt %)
Brinzolamide	1.0
Hydroxypropylmethylcellulose	0.5
Dibasic Sodium Phosphate	0.2
Disodium Edetate	0.01
Sodium Chloride	0.8
Purified Water	q.s
Benzalkonium Chloride	0.01
Cremaphor	0.1
NaOH/HCl	pH 7.1

Example 5

The following two formulations can be used concomitantly, within 30 minutes, or offset by more than 1 hour.

Formulation A

Ingredient	Concentration (wt %)
Brinzolamide	1.0
Hydroxypropylmethylcellulose	0.5
Dibasic Sodium Phosphate	0.2
Disodium Edetate	0.01
Sodium Chloride	0.8
Purified Water	q.s
Benzalkonium Chloride	0.01
Cremaphor	0.1
NaOH/HCl	pH 7.1

Formulation B

Ingredient	Amount (wt%)
(+)-Isopropyl Fluprostenol	0.001
Monobasic sodium phosphate	0.05
Dibasic sodium phosphate (anhydrous)	0.15
Sodium chloride	0.75
Disodium EDTA (Edetate disodium)	0.05
Cremaphor EL	0.1
Benzalkonium chloride	0.01
HCl and/or NaOH	pH 7.3 - 7.4
Purified water	q.s. to 100%

Example 6

The following two formulations can be used concomitantly, within 30 minutes, or offset by more than 1 hour.

Formulation A

Ingredient	Concentration (wt %)
Brinzolamide	1.0
Hydroxypropylmethylcellulose	0.5
Dibasic Sodium Phosphate	0.2
Disodium Edetate	0.01
Sodium Chloride	0.8
Purified Water	q.s
Benzalkonium Chloride	0.01
Cremaphor	0.1
NaOH/HCl	pH 7.1

Formulation B

Ingredient	Amount (wt%)
Isopropyl [2R(1E,3R),3S(4Z),4R]-7-[Tetrahydro-2-[4-(3-chlorophenoxy)-3-hydroxy-1-butenyl]-4-hydroxy-3-furanyl]-4-heptenoate	0.01
Monobasic sodium phosphate	0.05
Dibasic sodium phosphate (anhydrous)	0.15
Sodium chloride	0.75
Disodium EDTA (Edetate disodium)	0.05
Cremaphor EL	0.1
Benzalkonium chloride	0.01
HCl and/or NaOH	pH 7.3 - 7.4
Purified water	q.s. to 100%

Example 7

The following two formulations can be used concomitantly, within 30 minutes, or offset by more than 1 hour.

Formulation A

Ingredient	Concentration (wt %)
Brinzolamide	1.0
Mannitol	3.3
Carbopol 974P	0.4
Tyloxapol	0.025
Benzalkonium Chloride	0.1% + 5%xs
Disodium EDTA (Edetate Disodium)	0.01
Sodium Hydroxide	pH 7.5 +/- .2
Hydrochloric Acid	pH 7.5 +/- .2
Sodium Chloride	0.25
Purified Water	q.s. to 100%

Formulation B

Ingredient	Amount (wt%)
(+)-Isopropyl Fluprostenol	0.005
Monobasic sodium phosphate	0.05
Dibasic sodium phosphate (anhydrous)	0.15
Sodium chloride	0.75
Disodium EDTA (Edetate disodium)	0.05
Cremaphor EL	0.1
Benzalkonium chloride	0.01
HCl and/or NaOH	pH 7.3 - 7.4
Purified water	q.s. to 100%

Exampl 8

The following two formulations can be used concomitantly, within 30 minutes, or offset by more than 1 hour.

Formulation A

Ingredient	Concentration (wt %)
Brinzolamide	1.0
Mannitol	3.3
Carbopol 974P	0.4
Tyloxapol	0.025
Benzalkonium Chloride	0.1% + 5%xs
Disodium EDTA (Edetate Disodium)	0.01
Sodium Hydroxide	pH 7.5 +/- .2
Hydrochloric Acid	pH 7.5 +/- .2
Sodium Chloride	0.25
Purified Water	q.s. to 100%

Formulation B

Ingredient	Amount (wt%)
Isopropyl [2R(1E,3R),3S(4Z),4R]-7-[Tetrahydro-2-[4-(3-chlorophenoxy)-3-hydroxy-1-butenyl]-4-hydroxy-3-furanyl]-4-heptenoate	0.01
Monobasic sodium phosphate	0.05
Dibasic sodium phosphate (anhydrous)	0.15
Sodium chloride	0.75
Disodium EDTA (Edetate disodium)	0.05
Cremaphor EL	0.1
Benzalkonium chloride	0.01
HCl and/or NaOH	pH 7.3 - 7.4
Purified water	q.s. to 100%

We claim:

1. A method for lowering IOP in persons suffering from glaucoma or ocular hypertension, which comprises, administering topically to the eye a pharmaceutically effective amount of a prostaglandin and a carbonic anhydrase inhibitor.

2. The method of Claim 1 wherein the prostaglandin is (+)-isopropyl fluprostenol.

3. The method of Claim 1 wherein the prostaglandin is isopropyl [2R(1E,3R),3S(4Z),4R]-7-[tetrahydro-2-[4-(3-chlorophenoxy)-3-hydroxy-1-butenyl]-4-hydroxy-3-furanyl]-4-heptenoate.

4. The method of Claim 1 wherein the carbonic anhydrase inhibitor is brinzolamide.

5. The method of Claim 1 wherein the prostaglandin is (+)-isopropyl fluprostenol and the carbonic anhydrase inhibitor is brinzolamide.

6. The method of Claim 1 wherein the prostaglandin is isopropyl [2R(1E,3R),3S(4Z),4R]-7-[tetrahydro-2-[4-(3-chlorophenoxy)-3-hydroxy-1-butenyl]-4-hydroxy-3-furanyl]-4-heptenoate and the carbonic anhydrase inhibitor is brinzolamide.

INTERNATIONAL SEARCH REPORT

Intern[illegible]plication No
PCT/US 97/15793

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/557 A61K31/54

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 501 678 A (UENO SEIYAKU OYO KENKYUJO KK) 2 September 1992 see page 4, line 11-19; claims 1,2,11 see page 3, line 17-20; examples see page 5, line 25-26 see page 7, line 27-36 ---	1-6
X	DATABASE EPODOC EPO 1993 MERCK & CO: "Ophthalmic Compositions Comprising Combinations of a Carbonic Anhydrase Inhibitor and a Prostaglandin or Prostaglandin Derivative" XP002052576 & CN 1 075 634 A (MERCK & CO) See Title --- -/--	1

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
3 March 1998	19.03.98

Name and mailing address of the ISA	Authorized officer
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Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Inte l Application No
P 97/15793

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	HOYNG, RULO, GREVE ET AL: "The Additive IOP-Lowering Effect of Latanoprost in Combined Therapy with Other Ocular Hypotensive Agents" SURVEY OF OPHTHALMOLOGY, vol. 41, no. S2, February 1997, pages S93-S98, XP002052573 see page S96, left-hand column; table 1 ---	1
X	EP 0 590 786 A (ALCON LAB INC) 6 April 1994 see page 4, line 24-31; claim 9 ---	1
A	N. PFEIFFER: "The Potential for Topical CAI in Glaucoma Therapy" CURRENT OPINION IN OPHTHALMOLOGY, vol. 5, no. 2, April 1994, pages 20-25, XP002052574 see page 22, right-hand column, paragraph 2 ---	1
A	VON DER ELTZ: "Drug Therapy of Glaucoma: Old and New Agents" PHARMAZEUTISCHE ZEITUNG, vol. 141, no. 8, February 1996, pages 11-16,18, XP002052575 see page 16, left-hand column, paragraph 2 ---	1
A	US 5 378 703 A (ALCON LABORATORIES INC.) 3 January 1995 cited in the application see column 1, line 56-59; claim 7 ---	1,4-6
A	US 5 510 383 A (BISHOP JOHN E ET AL) 23 April 1996 cited in the application see claims 1,2,4,5; tables 1-3 ---	1,2,5
P,A	WO 97 23223 A (ALCON LAB INC) 3 July 1997 see page 9; claims 1-3; example 8 see page 40, line 26 - page 41, line 15 ---	1,3,6
A	EP 0 667 160 A (ALCON LABORATORIES INC.) 16 August 1995 cited in the application see page 2, line 25-46; claims 1,3,14 see example III; table 1 -----	1

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 97/ 15793

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: Claims 1-6
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 1-6 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 97/15793

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